

needed of the mechanism of action of ^{90}YIT in these diseases in the context of allogeneic transplantation.

How can the information in the Cassaday et al. study be used in clinical practice? The results of the current study confirm that the type of conditioning used in non-myeloablative transplantation strategies matters and that 1 size does not fit all. The results of this study and the study at our center suggest that ^{90}YIT should be more frequently administered to patients with active or refractory indolent lymphoma before transplantation. However, patients should be treated in clinical trials. The CLL results are intriguing and need to be confirmed in other studies. Contrary to previous findings in mouse models [6], it appears that prior exposure to rituximab does not affect the efficacy or safety of transplantation with ^{90}YIT .

Finally, this study does not address the lingering question in allogeneic transplantation: the incidence of graft-versus-host disease (GVHD). Over 70% of patients in this study developed acute II to IV GVHD. This incidence appears to be higher (23%) than observed in our transplantation study with ^{90}YIT [2], suggesting that the difference is related to the GVHD prophylaxis used rather than to the innate conditioning regimen. In this era of novel B cell receptor pathway-targeted agents, such as ibrutinib and idelalisib, it is paramount that the safety of allogeneic transplantation be enhanced to encourage referrals from the community.

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REFERENCES

1. Cassaday RD, Storer BE, Sorror ML, et al. Long-term outcomes of patients with persistent indolent B-cell malignancies undergoing non-myeloablative allogeneic transplantation. *Biol Blood Marrow Transplant.* 2014;21:281-287.
2. Khouri IF, Saliba RM, Erwin WD, et al. Nonmyeloablative allogeneic transplantation with or without ^{90}Y ibritumomab tiuxetan is potentially curative for relapsed follicular lymphoma: 12-year results. *Blood.* 2012;119:6373-6378.
3. Robinson SP, Goldstone AH, Mackinnon S, et al. Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. *Blood.* 2002;100:4310-4316.
4. Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. *J Clin Oncol.* 2008;26:5156-5164.
5. Jain N, Wierda W, Ferrajoli A, et al. A phase 2 study of yttrium-90-ibritumomab tiuxetan (Zevalin) in patients with chronic lymphocytic leukemia. *Cancer.* 2009;115:4533-4539.
6. Gopal AK, Press OW, Wilbur SM, et al. Rituximab blocks binding of radiolabeled anti-CD20 antibodies (Ab) but not radiolabeled anti-CD45 Ab. *Blood.* 2008;112:830-835.

Pretransplant Induction Regimens for Multiple Myeloma

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Vij et al. [1] for the Center for International Blood and Marrow Transplant Research (CIBMTR) report a retrospective database analysis of pretransplant depth of response and its impact on transplant outcomes. This article addresses some of the most complex problems facing not only transplanters but the greater myeloma community as well. Should we optimize pretransplant induction regimens to improve post-transplant remission duration and survival? A growing number of studies indicate that the depth of response pre-transplant correlates with post-transplant progression-free survival (PFS) and, in some studies, overall survival (OS) [2,3]. With the advent of technologies allowing the assessment of progressively lower burdens of disease, these correlations between depth of response and PFS and OS have become more profound and with this the inclination to intensify therapy to lessen the extent of minimal residual disease

(MRD) more compelling. More and more clinical trials are being designed in which patients with detectable MRD after the completion of therapy are shifted to alternative, often more intense regimens to eliminate the last vestiges of MRD. However, we have never definitively answered the question if doing more to achieve a greater depth of response, at the expenses of increased toxicity, impairment of quality of life, and potential loss of future treatment options, ultimately translates into improved outcomes. Prior studies do not address whether induction algorithms should include multiple regimens to achieve a greater response depth. Indeed, this is not limited to induction therapy but is pertinent to all myeloma care, including post-transplant consolidation and maintenance.

Thus, important questions are generated: How many cycles of induction therapy should we administer? Should we treat to maximum response with 1 induction regimen? Or, should we treat with sequential induction regimens until we achieve a "good" response? Additional pretransplant issues must be addressed, as they pertain to pretransplant depth of response. Three stem cell mobilization strategies—growth factor(s) alone, mobilizing chemotherapy that is not cytoreductive, and mobilizing regimens—are both cytoreductive and good mobilizers. The latter, obviously, also may improve the depth of response. If the overall goal is pretransplant response depth, then stem cell mobilization strategies should include cytoreductive mobilization regimens.

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Many of these issues are addressed in the study by Vij et al. reported in this issue of *Biology of Blood and Marrow Transplantation*. These authors gleaned from the CIBMTR database a group of 539 patients who had not achieved at least a partial response to first-line induction therapy. They then asked whether additional chemotherapy to improve induction responses pretransplant improves outcomes post-transplant. Thus, 324 patients received additional pretransplant “salvage” therapy, and these patients were compared with 215 patients who went directly to transplant without further treatment.

Bottom line, although 68% of the “salvage” cohort had improved response (only 8% complete response), these patients with deeper responses did not demonstrate improved PFS or OS in a multivariate analysis. The authors concluded that despite greater depth of response to “salvage” therapy pretransplant, patients did not have improved post-transplant outcomes. In contrast, the “control group” of patients who achieved at least a partial remission to induction therapy demonstrated superior PFS and OS, confirming that depth of response to one line of induction therapy correlates with favorable long-term outcomes.

There are inherent flaws and biases in retrospective database analysis. Some of the more relevant ones include the lack of a uniform induction/salvage regimen, number of cycles of induction/salvage, the lack of access in the earlier years of the study of proteasome inhibitors and/or newer immunomodulatory agents, the mobilization regimen (cytoreductive or not cytoreductive), and post-transplant maintenance. Regardless of these flaws, an important message has been generated by this study that will almost certainly immediately impact the clinical management of multiple myeloma patients eligible for transplant: In the absence of disease progression to first-line induction therapy, additional hammering of patients with sequential cycles of “salvage” chemotherapy should not be pursued. This large CIBMTR database analysis does not support “salvage” therapy to improve the depth of response pretransplant. Instead, patients should proceed to stem cell mobilization and subsequent transplant.

Are there possible exceptions to this statement? A study by the PETHEMA group demonstrated that patients with progressive disease to induction therapy have dismal outcomes when taken directly to transplant, with a median PFS of only 6 months [4]. Should these patients be diverted to other forms of therapy? Should they receive more intense salvage therapy pretransplant? These are extraordinarily complex questions. Is the failure to respond to induction therapy merely an exceptionally powerful prognostic variable or volume of disease issue that can be overcome with application of alternative treatment regimens? Is it possible

that the continued application of chronic therapy in the face of inherently resistant disease is a recipe for the selection of progressively even more resistant disease? Unfortunately, we have learned in myeloma that resistance to one leads, at some level, to resistance to all.

Another unanswered question not addressed by Vij et al. is the role of multiple cycles of high-dose therapy in patients who do not achieve optimal responses to first-line induction therapy. In the post-transplant setting, older studies (IFM 94 [5] and Bologna 96 [6]) indicated that patients not achieving deep responses (very good partial response in the IFM 94 and near complete response in the Bologna 96 studies) were those who derived the maximal benefit from tandem transplant. Extrapolating from this older dataset, in an era before the routine use of novel therapies, we should consider tandem autologous transplants in induction “failures” or, in the cytogenetic high-risk individual, participation in a clinical trial of an allogeneic transplant or autologous/allogeneic tandem transplant.

In summary, this study by Vij et al. [1] is one of the few efforts that legitimately addresses a profound philosophical question in myeloma care. Is doing more to achieve greater depth of response the ultimate goal of all therapy? Certainly, to biologically “cure” patients (ie, eliminate every single clonogenic cell) this has to be the goal. However, when treatment shows this is unlikely to happen, should we get to our best therapy as quickly as possible and avoid the reality of greater toxicity and the selection of increased resistance that is inherent in salvage therapy?

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REFERENCES

1. Vij R, Kumar S, Zhang MJ, et al. Impact of pre-transplant therapy and depth of disease response prior to autologous transplantation for multiple myeloma. *Biol Blood Marrow Transplant*. 2015;21:335–341.
2. Martinez-Lopez J, Lahuerta JJ, Pepin F, et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. *Blood*. 2014;123:3073–3079.
3. Rawstron AC, Child JA, de Tute RM, et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. *J Clin Oncol*. 2013;31:2540–2547.
4. Rosiñol L, García-Sanz R, Lahuerta JJ, et al. Benefit from autologous stem cell transplantation in primary refractory myeloma? Different outcomes in progressive versus stable disease. *Haematologica*. 2012;97:616–621.
5. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2003;349:2495–2502.
6. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. *J Clin Oncol*. 2007;25:2434–2441.